# Integrated Endocrinology

## Anterior Pituitary

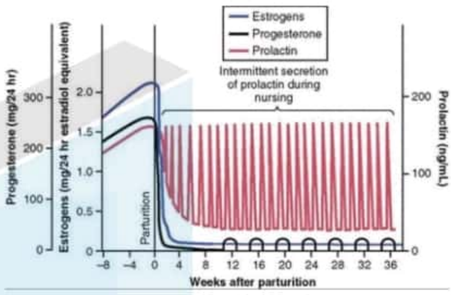
### PROLACTIN

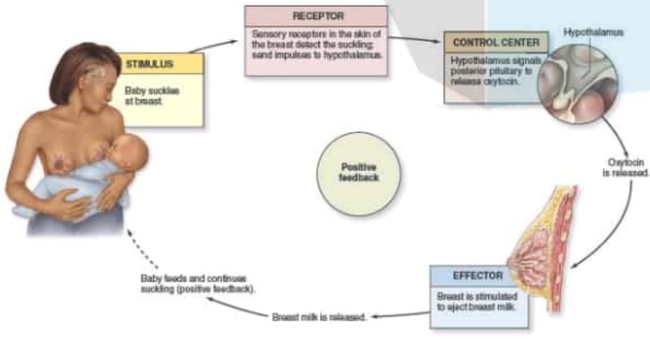
- Stimulus increasing prolactin secretion
  - Nursing
  - Pregnancy
  - Estrogen
  - Thyroid Releasing Hormone (Hypothyroidism)
  - Sleep- NREM, stages 3/4
  - Strenuous exercise
  - Stress (not a typical stress hormone)
  - Sexual intercourse, Breast stimulation
  - Opiates
  - Phenothiazines
- Prolactin increases during pregnancy along with Estrogen and progesterone
- Prolactin suddenly falls after delivery followed by spikes during nursing. These spikes are up to 3 months after which there are no spikes even on nursing.
- Prolactin takes up to 8 days postpartum to come back to pre-pregnant levels
- Dopamine inhibits prolactin release.
- There is a positive feedback loop between oxytocin and prolactin during breast suckling.

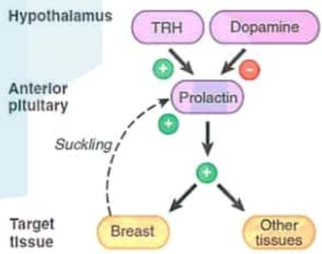
Typical Stress hormones are:

- Glucocorticoids
- Glucagon
- Catecholamines
- Growth Hormone
- ADH

All stress hormones increase blood levels of glucose & FFA





RECEPTOR
Sensory receptors in the skin of the breast detect the suckling; send impulses to hypothalamus.
CONTROL CENTER
Hypothalamus signals posterior pituitary to release oxytocin.
Hypothalamus
STIMULUS
Baby suckles at breast.
Positive feedback
Oxytocin is released.
EFFECTOR
Breast is stimulated to eject breast milk.
Baby feeds and continues suckling (positive feedback).
Breast milk is released.




Prolactin causes milk secretion from the breast after estrogen and progesterone priming

Prolactin increases mRNA levels and subsequent production of casein and lactalbumin

### HYPERPROLACTINEMIA (PROLACTINOMA)

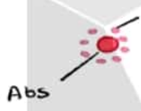
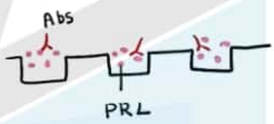
**Males:** Lethargy, Reduced Libido, Galactorrhea (Late), Impotence

**Females:** Galactorrhea, Infertility (M/C), Amenorrhea

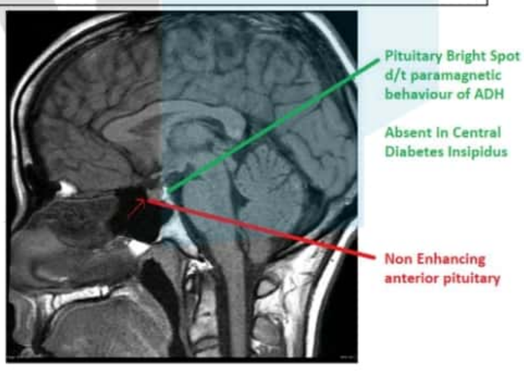
Compressive symptoms in both (Macroadenoma >10mm) → Bitemporal heminopia

Work-up of Prolactinoma:

- Serum PRL
  - Normal
    - Males: 10-20 microgram/litre
    - Females: 10-25 microgram/litre
  - Increased
    - 25- 40 – Physiological – Pregnancy, Lactation, Chest Wall Stimulation, Stress, NREM Sleep
    - 25-100 – Hypothalamic Pituitary stalk lesion, Iatrogenic
    - >200 – PROLACTINOMA

| MACROPROLACTENEMIA | HOOK EFFECT |
| --- | --- |
| • High Prolactin in Asymptomatic patient | • Normal Prolactin in Symptomatic patient |
| • Aggregation of PRL via crosslinking by IgG ab   | • Very high PRL saturates Reagent Abs   |
| • Large PRL –Bio inactive<br>✓ PEG detects it | ✓ Repeat test in 1:100 dilution |

**IOC → MRI**

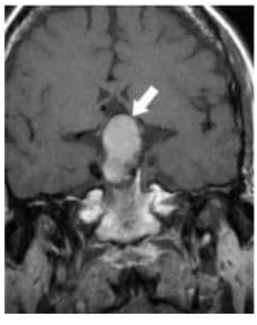

Pituitary Bright Spot d/t paramagnetic behaviour of ADH
Absent in Central Diabetes Insipidus
Non Enhancing anterior pituitary

**Pituitary macroadenoma**

'Figure of 8' or 'snowman appearance'

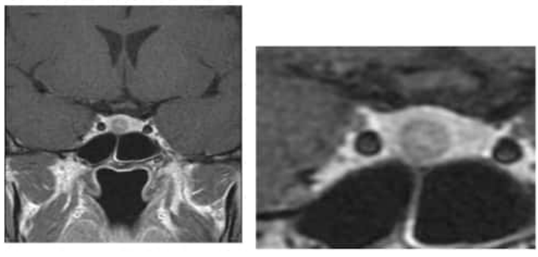
Because of central indentation by diaphragma sellae

And 'ballooning' of the sellar cavity



**Pituitary microadenoma (<10mm)**

**Dx: on Dynamic MRI** : a rounded region of delayed enhancement compared to the rest of the gland

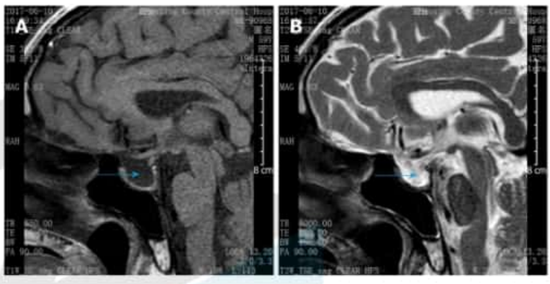


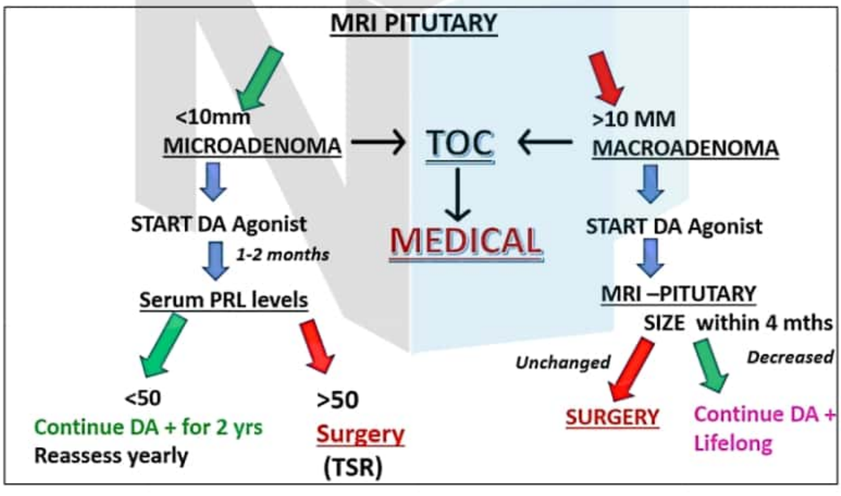
**Empty Sella Syndrome**

It is the condition when the pituitary gland shrinks or becomes flattened, filling the sella turcica with cerebrospinal fluid instead of the normal pituitary.

MRI: Empty Ballooned Sella

Cause: Pituitary destroying tumour, Idiopathic Intracranial HTN, Congenital absence of sella turcica (rare).




DOC for PROLACTINOMA

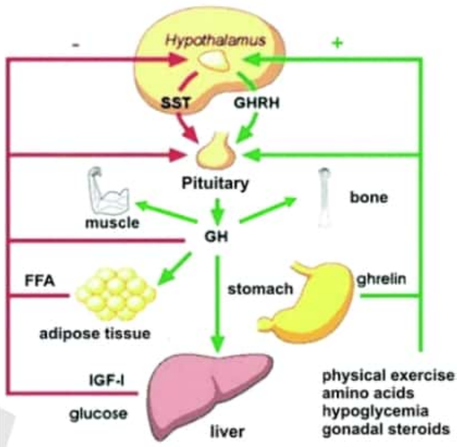
- Non pregnant female: Cabergoline
- Pregnant Female- Bromocriptine
- Males: Cabergoline
- If with visual defect: Medical t/t

DOC FOR HYPERPROLACTINEMIA in a fertile female- Bromocriptine

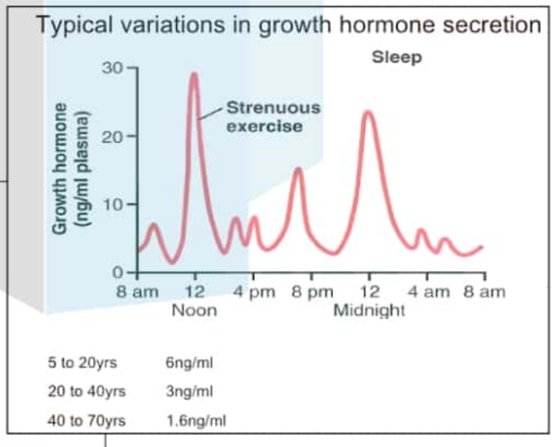
## GROWTH HORMONE

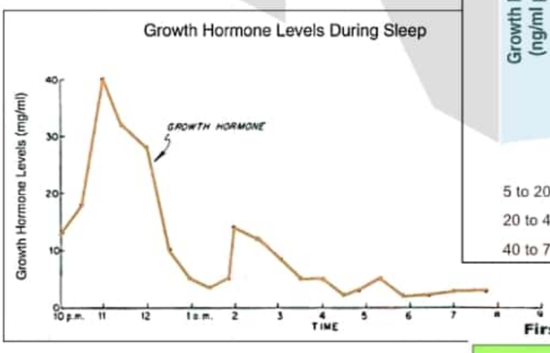
- Major regulator of GH is GHRH
- Ghrelin is increased in fasting states and further increases GH
- GH acts on liver to produce IGH-1
- Stimuli to <u>increase</u> the GH secretion:

| |
|---|
| • Hypoglycemia |
| • Stress |
| • Exercise |
| • Fasting |
| • Ghrelin |
| • Increase in circulating levels of certain amino acids; infusion of arginine |
| • Protein meal |
| • Glucagon |
| • Lysine vasopressin |
| • Sleep |
| • L- DOPA |
| • Apomorphine, Dopamine agonists |
| • Estrogens and androgens |
| • pyrogen |




- Factors that <u>decrease</u> the GH secretion:
  - REM Sleep (NREM Sleep increases)
  - Glucose, Cortisol, FFA [Direct action of cortisol is to decrease GH, though both are increased in times of stress]
  - Medroxyprogesterone
  - GH and IGF -1



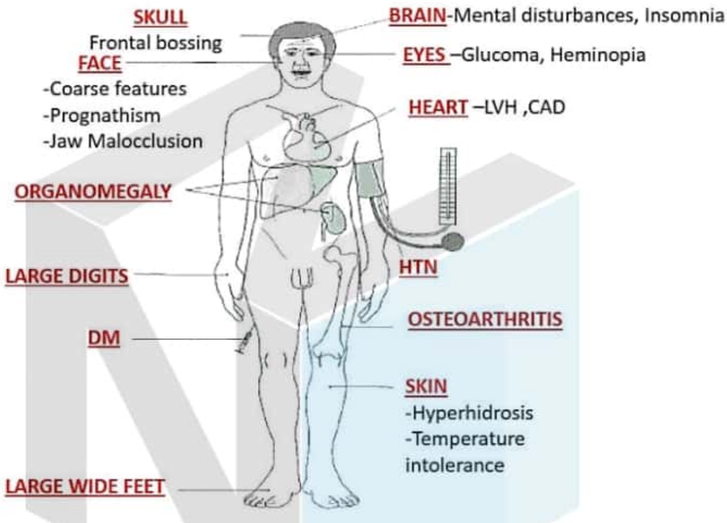
- **Actions of Growth Hormone :**
- Indirect actions are mediated via IGF-1
- Growth spurt of puberty is d/t IGF-1

Direct actions
- Increases blood glucose ("anti- insulin")
- Increases FFA level; ketogenic
- Increases protein synthesis
- Increases sodium retention
- Epiphyseal growth

Indirect actions
- Decreases blood glucose
- Lipogenesis
- Protein synthesis
- Chondrogenesis
- Epiphyseal growth

- GH and IGF-1 also have synergistic action on epiphysis growth: GH increases the number of receptors of IGF-1 on epiphysis.

**ACROMEGALY**




**XRAY:** Hyper-pneumatization of Frontal Sinus, Prognathism, Ballooning of the sella, **spade like phalanges (d/t widening of joint space because of cartilage hypertrophy) leading to premature ostero-arthritis.**

**Foot XRAY:** Heel pad thickness increases

**GH** is never done in investigations due to its short half-life and pulsatile secretion,

## WORK UP

- **SCREENING TEST** — Serum IGF-1 levels
- **CONFIRMATORY TEST** — GH SUPPRESSION TEST
- **ETIOLOGY** — MRI PITUITARY
  - M.C.C –Somatotrophic adenoma

## MANAGEMENT OF ACROMEGALY

**TOC – TSR**

GOALS
- ✓ GH –Normal on post op D1
- ✓ IGF-1 –Normal @12 weeks
- ✓ MRI Repeat @12 weeks

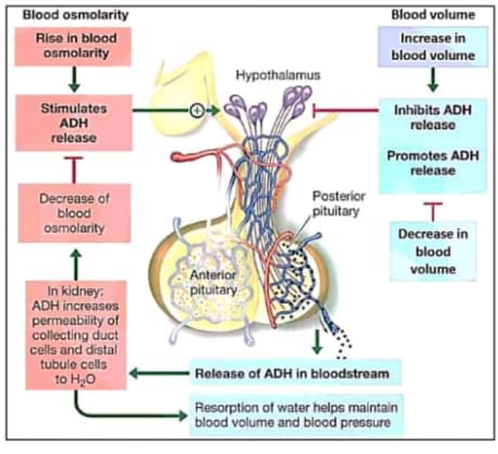
**REASSESS**

- **REMISSION** → Annual IGF-1, GH LEVELS, GH suppression test → MRI if clinical/biochem signs reoccur
- **INCOMPLETE REMISSION** → **MEDICATIONS**
  - SPECIAL CONSIDERATIONS: -Tumour unresectable, -Poor Surgical Candidate
  - NO RESPONSE → RADIOTHERAPY
  - SOMATOSTATIN ANALOGUE: -Octreotide(s/c), -Lanreotide(i/m)
  - GH ANTAGONIST: PEGVISOMANT(S/C)

## ANTI-DIURETIC HORMONE (ADH)

- Neurosecretion: ADH, Oxytocin (Supraoptic-SO, Paraventricular-PV nuclei of the hypothalamus)
- ADH: 5/6th from SO, 1/6th from PV
- Oxytocin: 1/6th from SO, 5/6th from PV

- **Increase in plasma osmolarity** as less as 5 mOsm/L in cases like normal sweating can stimulate the release of ADH. **(MORE SENSITIVE than blood volume)**


Blood osmolarity
Rise in blood osmolarity
Stimulates ADH release
Decrease of blood osmolarity
In kidney: ADH increases permeability of collecting duct cells and distal tubule cells to $H_2O$
Blood volume
Increase in blood volume
Inhibits ADH release
Promotes ADH release
Decrease in blood volume
Hypothalamus
Posterior pituitary
Anterior pituitary
Release of ADH in bloodstream
Resorption of water helps maintain blood volume and blood pressure

- **Hypovolemia/Loss of blood Volume:** of minimum 10% will also stimulate ADH release.
- **Stimuli which increase ADH Secretion:**
  - Increase in plasma osmolarity
  - Decrease in blood volume
  - Stress
  - Angiotensin 2
  - Prolonged standing
- **Stimuli which decrease ADH secretion:**
  - Decrease in plasma osmolarity
  - Increase in blood volume
  - Alcohol intake
- Precursor Molecule:
  PREPROPRESSOPHYSIN

| | | |
|---|---|---|
| 1 | Signal peptide | 19 aa |
| 2 | Vasopressin | 9 aa |
| 3 | Neurophysin II | 95 aa |
| 4 | Glycopeptide | 39 aa |

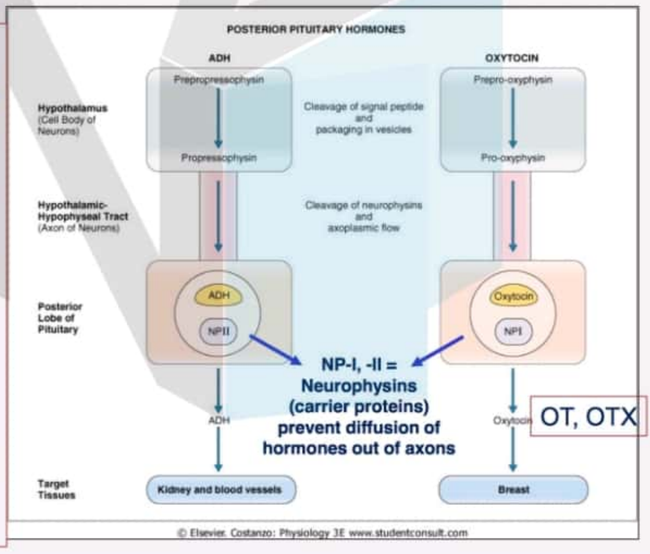
Synthesis of posterior pituitary hormones

**-ADH and OT originate from the same chromosome**

-During intraaxonal transport, precursor hormone is cleaved into ADH (or oxytocin), NP, and a terminal glycoprotein

-NP arranges into tetramers that bind 5 ADH

-All fragments are secreted into the plasma




| Receptor | Second messenger | Location | Actions |
|---|---|---|---|
| **V1/ V1A** | GPCR;<br>Phosphatidylinositol &<br>Ca | VSM<br>Heart<br>Liver<br>Area postrema<br>Platelet | Vasoconstriction<br>Myocardial hypertrophy<br>Glycogenolysis<br>Decreases cardiac output<br>Platelet aggregation |

| | | | |
|---|---|---|---|
| **V2** | GPCR; cAMP | Collecting ducts<br>Vascular endothelium | Increase insertion of Aquaporin 2 on luminal membrane to increase water reabsorption<br>Release of Von Willebrand factor & factor VIII |
| **V3/ V1B** | GPCR; Phosphatidylinositol & Ca | Anterior pituitary | Increases secretion of ACTH, PRL, endorphins |

**DIABETES INSIPIDUS**

## CAUSES OF NEPHROGENIC DI

**Go C O V I D Go**

**Go**-Genetic
**C** –**C**arcinoma –Sarcoma,**C**alcium
**O** –**O**bstruction –Ureteric
**V** –**V**ascular –Sickle cell ,Ischemia(ATN)
**I** -Infiltrative –Amyloidosis
**D** –**D**rugs
**Go**-Granu**lo**ma-Sarcoidosis

**DRUGS**

**ABCD FoR My Life**
- ✓ **A** –Aminoglysoside
- ✓ **B**-Amphotericin **B**
- ✓ **C**-Cisplatin
- ✓ **D**-**D**emecocylcine
- ✓ **Fo**-**Fo**scarnet
- ✓ **R** –**R**ifampicin
- ✓ **My**-**M**ethoxyflurane
- ✓ **Life** –**Li**

## CAUSES OF CENTRAL DI

**B I N O D - 3 I DIOTS**

**B**irth –Genetic- AD>AR (Wolfram syndrome /DIDMOAD )

**I**DIOPATHIC (>50 %)
**I**NFECTION –Meningitis ,Encephalitis
**I**nflammation –Wegners,Lupus

**N**EOPLASM –Primary(CNS) ,Secondaries
**O**-t**O**xins –Snake venom ,tetradoxin
**D**amage – Head Injury/surgery

## POLYURIA

>3L/day ;>40 ml/kg/day

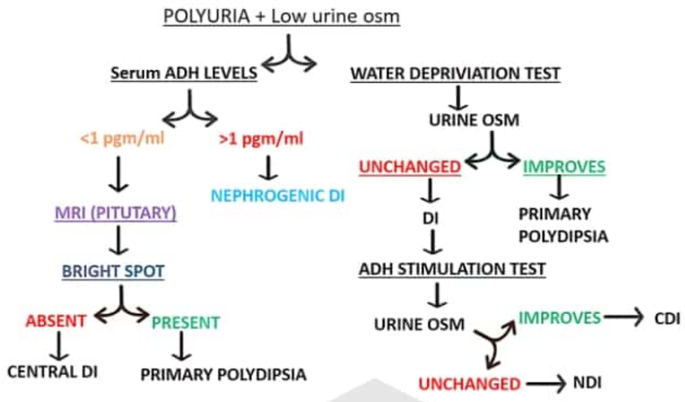
↓

**Urine osmolarity**

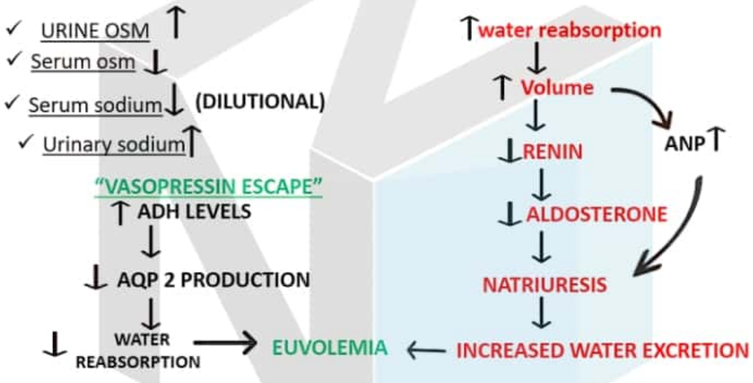
**<300 mosm/L** ← → **>300 mosm/L**

**SOLUTE/OSMOTIC DIURESIS**
- ✓ **Glucose**
- ✓ **Mannitol**
- ✓ **Calcium**

- ➢ **DIABETES INSIPIDUS**
- ➢ **PRIMARY POLYDYPSEA**




## SIADH




## CAUSES OF SIADH

**S I A D H**

**S-Sepsis**

**I-Infarct cerebral –arterial/venous**

**A-Anomaly-agenesis of corpus callosum**

**D-Drugs**

**H-Head trauma**

DRUGS CAUSING SIADH

"**SIADH Causes Poor Voiding**"

**S**: SSRIs (Sertaline)

**I**: Indomethacin (Analgesics)

**A**: Antidepressants (Tricyclics)

**D**: Diuretics (Thiazides)
Desmopressin

**H**: Hormone –Oxytocin(high dose)

**Causes**:Cyclophosphamide
Carbamazepine

**Poor**: Phenothiazines

**Voiding**:Vincristine

**AIR VOIDING**

# TREATMENT OF SIADH

**WATER RESTRICTION (TOC)**

Urine :plasma electrolyte ratio

$$\frac{Ur.Na^+ + Ur.K^+}{Plasma\ Na^+}$$

- **>1** — <500 ml/day
- **1** — 500-700 ml/day
- **<1** — < 1 L/day

**SODIUM Correction**

$Na^+$ deficit =0.6 X Body weight X (Target $Na^+$ - Serum $Na^+$ )

Correction @<8-10 meq/L over 24 hours

**ADH ANTAGONIST**

- **DEMECOCYCLINE**
- **VAPTANS** (DOC)
  - **TOLVAPTAN (ORAL) V2-** *-HEPATOTOXIC*
  - **CONIVAPTAN (INJECTABLE)V1/V2** *-Can cause HypoTN*

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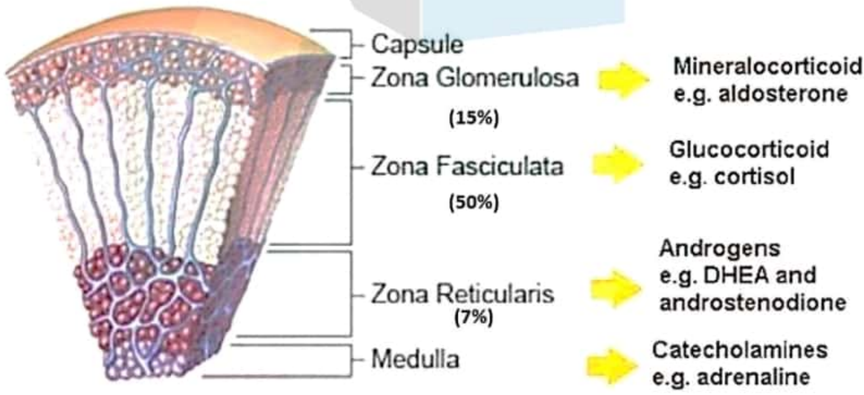
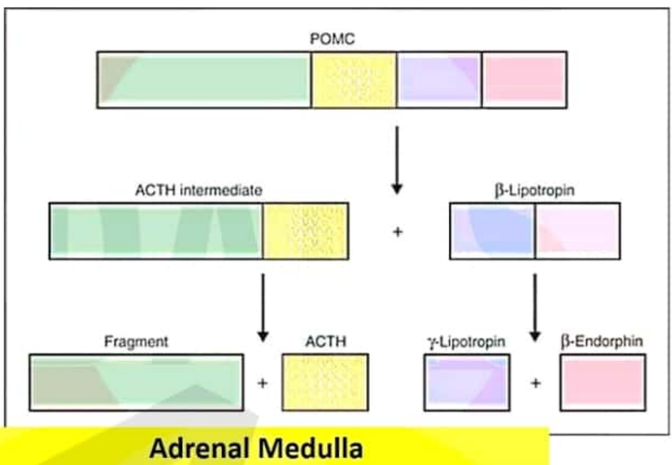
## ADRENAL



**ACTH SYNTHESIS**

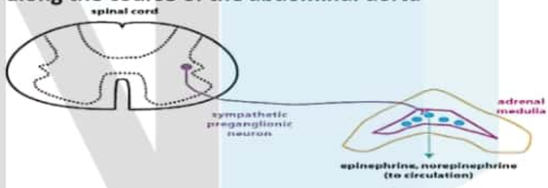
**POMC**: PRE-OPIO-MELANO-CORTIN

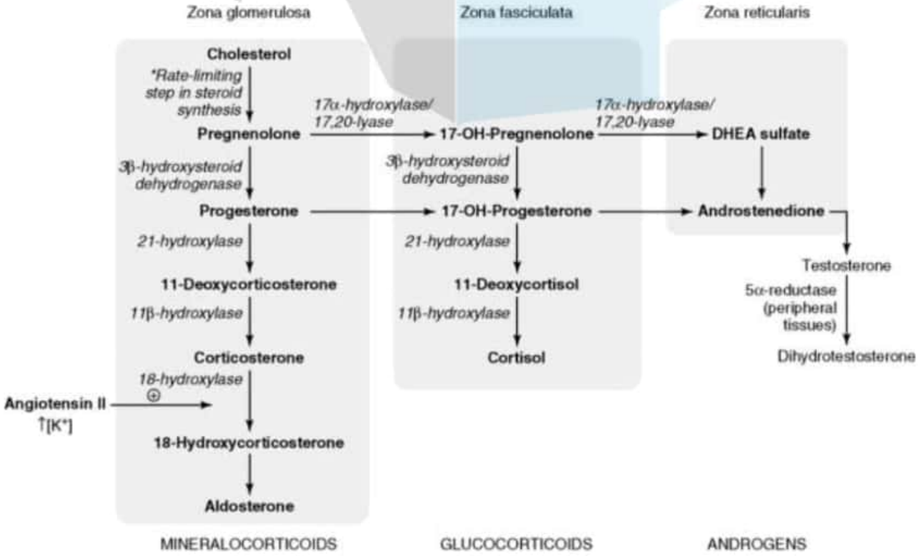
ALPHA & GAMMA MSH is negligibly found in Humans due to rudimentary intermediate lobe of pituitary gland.




## Adrenal Medulla

- ***Modified sympathetic ganglion*** **comprising *30%* of the adrenal gland**
- **Richly innervated by *pre - ganglionic, cholinergic, sympathetic nerve fibres***
- **Approximately *90%* of cells - *epinephrine* secreting**
  ***Remainder* - *norepinephrine* secreting**
- **Medullary tissue is also located at *extra-adrenal* sites along the course of the *abdominal aorta***

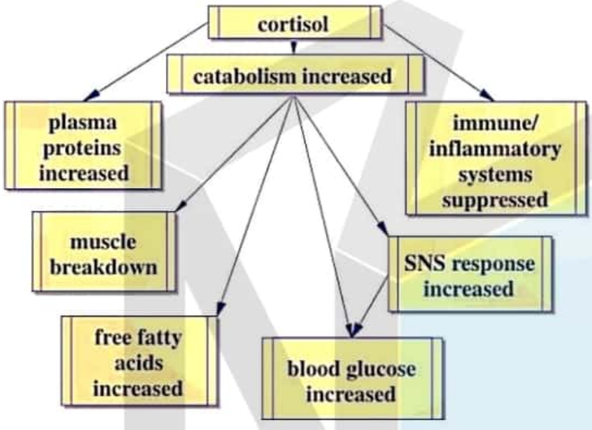


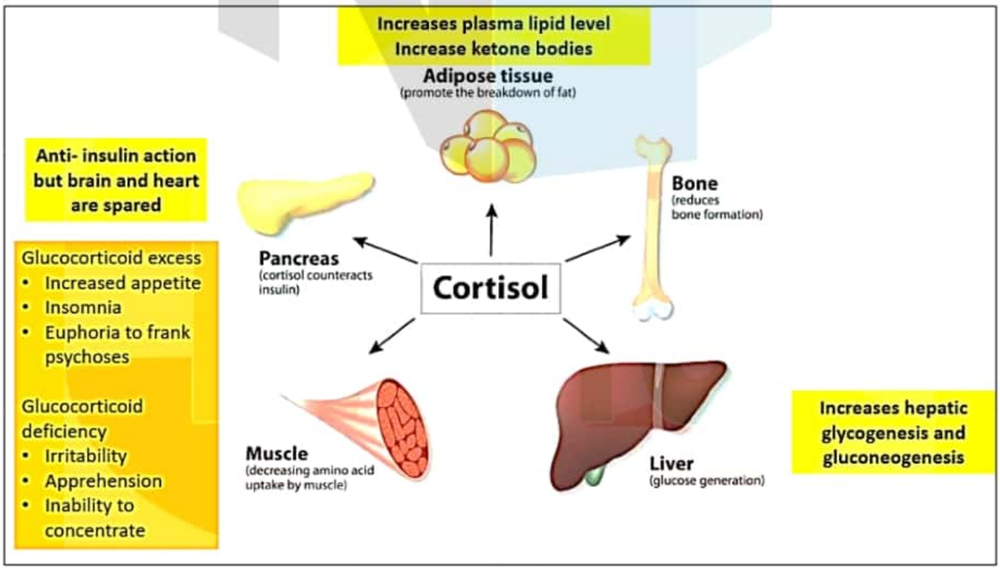
| Deficiency | Aldosterone | Cortisol | Androgens |
|---|---|---|---|
| 21β | ↓ | ↓ | ↑ |
| 11β | ↓ | ↓ | ↑ |
| 17α | ↑ | ↓ | ↓ |
| 17,20-lyase | ↑ | ↑ | ↓ |

**CORTISOL**

## Actions of cortisol

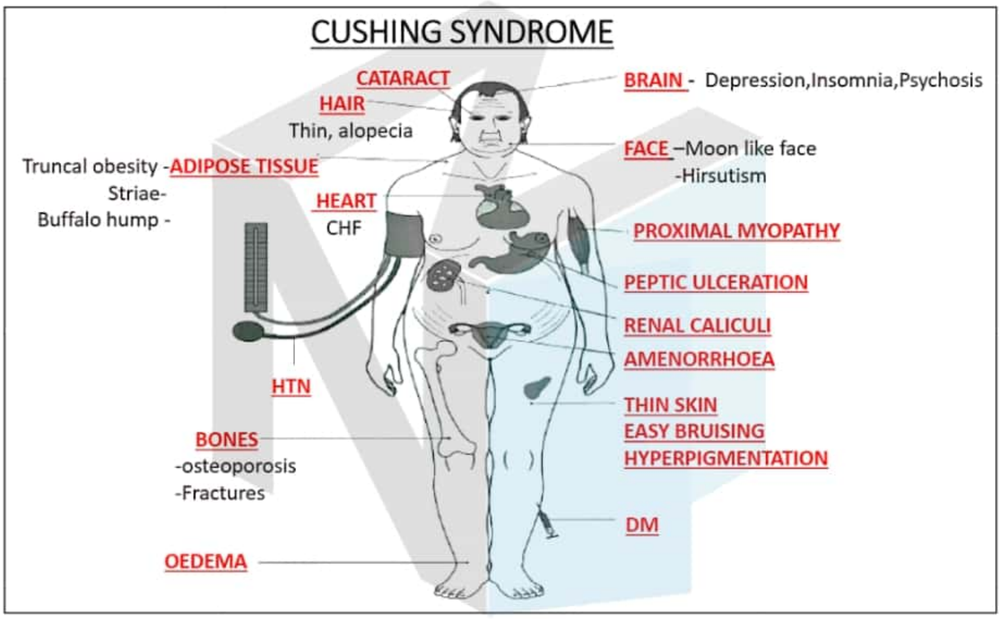



- Reduce
  B- Basophils
  E- eosinophils
  L- Lymphocytes
- Increase neutrophils, monocytes, RBCs and platelets



- Glucocorticoids have a permissive action on
- Glucagon
  - Glycogenolysis
  - Lipolysis
- Catecholamines
  - Glycogenolysis
  - Lipolysis
  - Bronchodilation
  - Pressor action

**CUSHING'S DISEASE**




## SCREENING TEST

✓ **24 HR URINARY CORTISOL EXCRETION (3 times above normal)**

✓ **DEXAMETHASONE OVERNIGHT TEST**
(Plasma cortisol >50nmol/L @ 8-9 am after 1mg dexa@11 pm )

✓ **MIDNIGHT PLASMA CORTISOL >130 nmol/L**
or
✓ **MIDNIGHT SALIVARY CORTISOL >5 nmol/L**

## CONFIRMATORY TEST

LOW DOSE DEXA TEST

Plasma cortisol >50 nmol/L after 0.5 mg dexamethasone 6 hrly for 2 days

## ETIOLOGY ?

PLASMA ACTH LEVELS

**ACTH HIGH**
>15 pg/ml

**ACTH LOW**
< 5 pg/ml

**ACTH DEPENDENT CUSHING**
- ✓ PITUTARY ADENOMA
- ✓ ECTOPIC ACTH

**ACTH INDEPENDENT CUSHING**
ADRENAL
-ADENOMA
-HYPERPLASIA
-CARCINOMA

## ACTH INDEPENDENT CUSHING

CT (ABDOMEN)

BILATERAL MICRO/MACRO ADRENAL HYPERPLASIA → BILATERAL ADRENALECTOMY

UNILATRAL ADRENAL MASS → ADRENAL TUMOR WORKUP → UNILATERAL ADRENELECTOMY

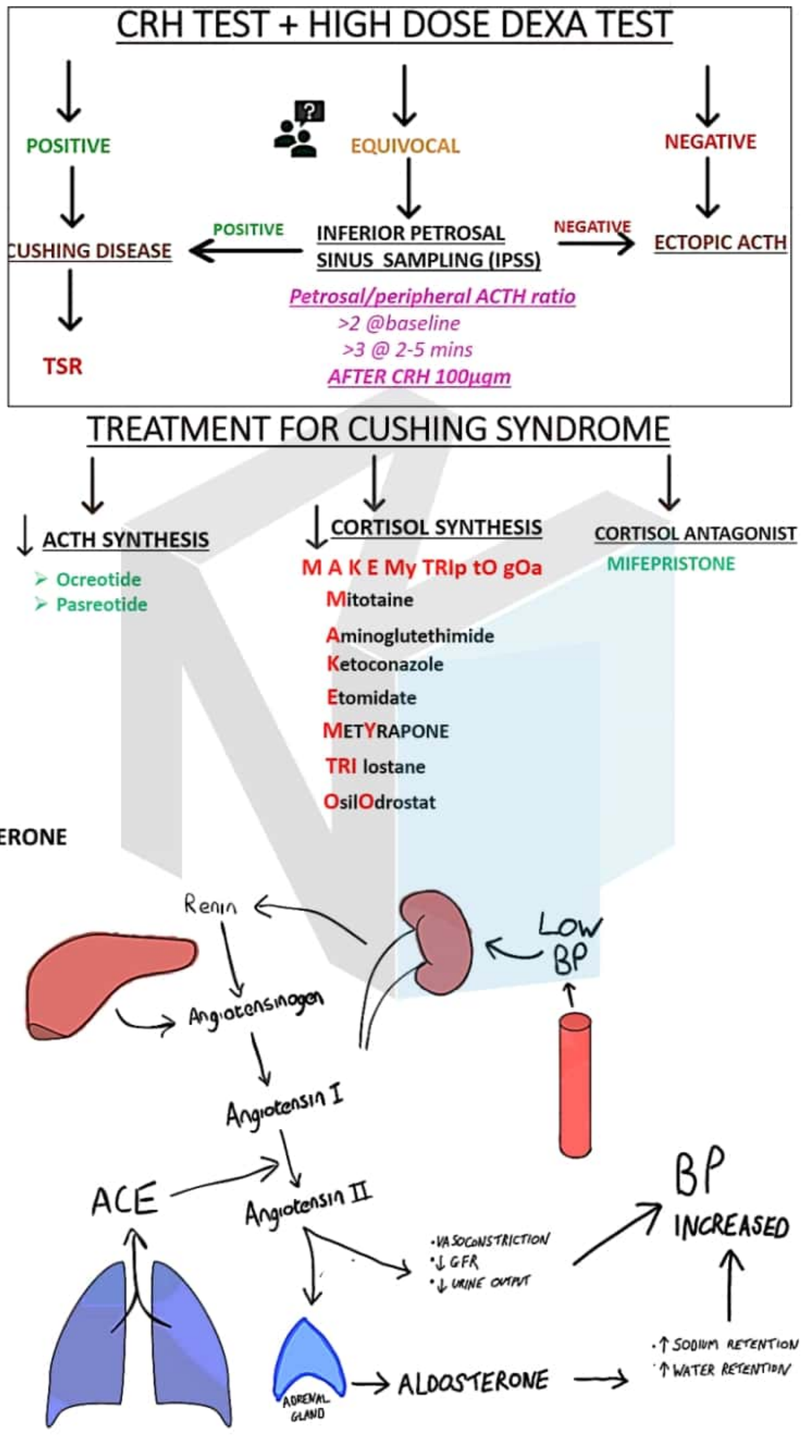
## ACTH DEPENDENT CUSHING

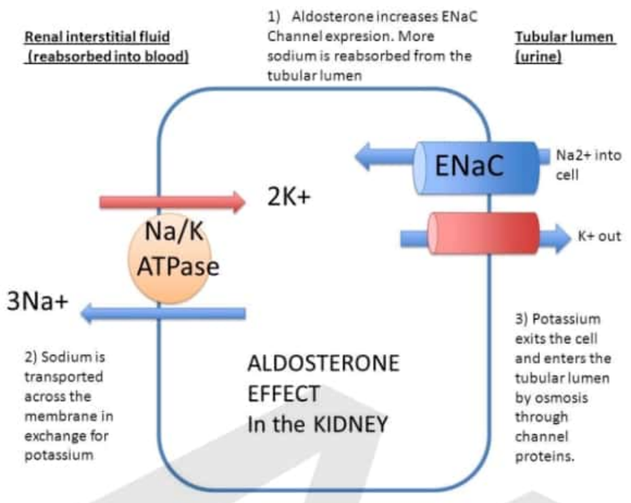
CRH TEST

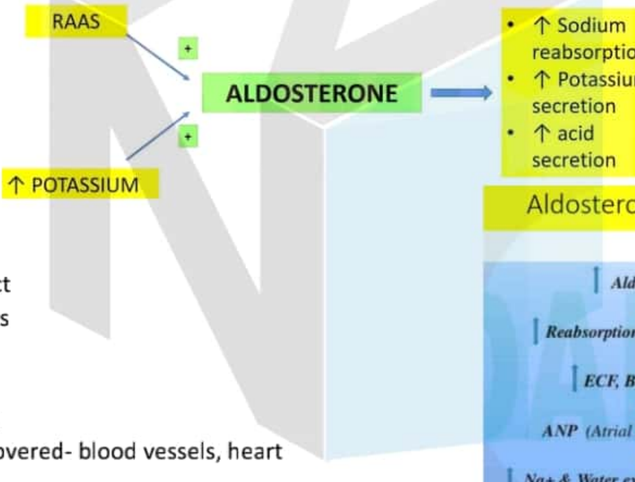
ACTH increase >40 % @15-30 min
+
Cortisol increase >20 % @45-60 mins after i/v CRH 100 µgm

HIGH DOSE DEXA TEST

Cortisol suppression >50% after 2mg dexa 6 hrly for 2 days


CRH TEST + HIGH DOSE DEXA TEST
POSITIVE
EQUIVOCAL
NEGATIVE
CUSHING DISEASE
POSITIVE
INFERIOR PETROSAL SINUS SAMPLING (IPSS)
NEGATIVE
ECTOPIC ACTH
Petrosal/peripheral ACTH ratio
>2 @baseline
>3 @ 2-5 mins
AFTER CRH 100µgm
TSR
TREATMENT FOR CUSHING SYNDROME
ACTH SYNTHESIS
Ocreotide
Pasreotide
CORTISOL SYNTHESIS
M A K E My TRIp tO gOa
Mitotaine
Aminoglutethimide
Ketoconazole
Etomidate
METYRAPONE
TRI lostane
OsilOdrostat
CORTISOL ANTAGONIST
MIFEPRISTONE
ALDOSTERONE
Renin
Low BP
Angiotensinogen
Angiotensin I
ACE
Angiotensin II
•VASOCONSTRICTION
•↓ GFR
•↓ URINE OUTPUT
BP INCREASED
•↑ SODIUM RETENTION
•↑ WATER RETENTION
ADRENAL GLAND
ALDOSTERONE


Renal interstitial fluid (reabsorbed into blood)
1) Aldosterone increases ENaC Channel expresion. More sodium is reabsorbed from the tubular lumen
Tubular lumen (urine)
ENaC
Na2+ into cell
2K+
Na/K ATPase
K+ out
3Na+
2) Sodium is transported across the membrane in exchange for potassium
ALDOSTERONE EFFECT In the KIDNEY
3) Potassium exits the cell and enters the tubular lumen by osmosis through channel proteins.

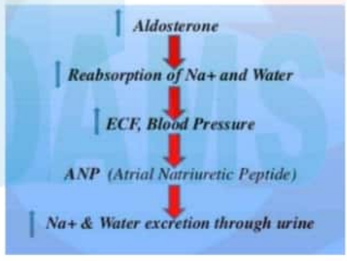



Aldosterone Receptors:

- Collecting duct
- Salivary glands
- Sweat glands
- Colon
- Hippocampus
- Recently discovered- blood vessels, heart

ANP is secreted on stimulation of Cardiopulmonary stretch receptors

Aldosterone escape




## HYPERALDOSTERONISM

SECONDARY
↓ VOLUME
↑ RENIN
↑ ALDOSTERONE
↑ Na + water reabsorption
VOLUME NORMAL

PRIMARY
- B/L IDIOPATHIC CORTICAL HYPERPLASIA (60%)
- ADRENAL ADENOMA (40%)

M.C.C of CONN syndrome
ADRENAL ADENOMA

## CLINICAL SUSPICION OF HYPERALDOSTERONISM

SEVERE HTN (>3 drugs,drug resistant)
OR
HYPOKALEMIA
OR
ADRENAL MASS
OR
FAMILY HISTORY OF EARLY ONSET HTN /CVA @<40 ye

**SCREENING TEST**

ALDOSTERONE RENIN RATIO (ARR) ↑

↑ ALDOSTERONE
↓
↑ VOLUME
↓
↓ RENIN

**CONFIRMATORY TEST**

- SALINE INFUSION TEST
- ORAL Na loading
- Fludrocortisone suppression

↑ VOLUME
↓
NO SUPRESSION OF ALDOSTERONE

**ETIOLOGY**

CT ADRENALS

UNILATERAL ADRENAL MASS ↔ BILATERAL ADRENAL HYPERPLASIA

BILATERAL ADRENAL HYPERPLASIA → DRUG TREATMENT

UNILATERAL ADRENAL MASS → AGE <40 years / AGE >40 years

AGE <40 years → UNILATERAL ADRENALECTOMY

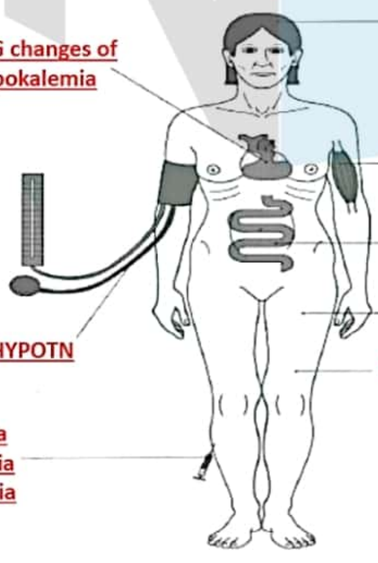
AGE >40 years → ADRENAL VENOUS SAMPLING

ADRENAL VENOUS SAMPLING → POSITIVE / NEGATIVE

POSITIVE → UNILATERAL ADRENALECTOMY

NEGATIVE → DRUG TREATMENT

## ADISSON DISEASE



ECG changes of Hypokalemia

BRAIN
-Lethargy
-Depression
-Dizziness

-Muscle weakness
-Fatigue

INTESTINES –Abdominal pain,nausea
-Constipation,Anorexia

WEIGHT LOSS

SKIN
Hyperpigmentation

HYPOTN

-Hyponatremia
-Hyperkalaemia
-Hypoglycaemia

| ADRENAL INSUFFECIENCY | PRIMARY | SECONDARY |
|---|---|---|
| INCIDENCE | 2 in 10,000 | 3 in 10,000 |
| ETIOLOGY | TB,AUTOIMMUNE | HPA disorder |
| GC Deficiency | + | + |
| MC Deficiency | + | - |
| ADRENAL ANDROGEN DEFN. | + | - |
| SALT CRAVING POSTURAL HYPOTN | + | - |
| HYPERPIGMENTATION | + | - (ALBASTER SKIN) |
| LOSS OF AXILLARY/PUBIC HAIR | + | +/- |
| VITILIGO | + | - |
| ACTH | ↑ | ↓ |
| Serum $Na^+$ | ↓ | NORMAL |
| SERUM $K^+$ | ↑ | NORMAL |

## SCREENING/CONFIRMATION TEST

**COSYNTROPIN TEST**

250 µgm Cosyntropin

↓ 30-60 mins

Plasma cortisol <450-500 nmol/L

## DIFFERENTIAL DIAGNOSIS

↑ACTH
↑RENIN
↓ALDOSTERONE
→ **PRIMARY**

**SECONDARY** → **MRI (Pituitary)**

NORMAL RENIN,ALDOSTERONE
↓ACTH

**POSITIVE** → HYPOTHALAMIC PITUTARY MASS LESION

**NEGATIVE** → -H/O STEROID THERAPY -HEAD INJURY

**ADRENAL AUTOANTIBODIES**

**POSITIVE** → -AUTOIMMUNE ADRENALITIS -AUTOIMMUNE POLYGLANDULAR SYNDROME (APS)

**NEGATIVE** →
ADRENAL CT –TB,Hemmorhage,Lymphoma
SERUM 17OHP –Congenital Adrenal Hyperplasia

# PHAEOCHROMOCYTOMA

HEADACHE (M.C)

DIAPHORESIS + PALPITATION

+

HTN

SUSTAINED (M.C) / PAROXYSMAL (Characteristic )

MAJOR CATECHOLAMINES SECRETED

NORMAL: EPINEPHERINE >NE

PHAEOCHROMOCYTOMA: NE>EPINEPHERINE

✓ Extra Adrenal Phaeo –ONLY NE

✓ Malignant Phaeo

DOPAMINE >NE>EPINEPHERINE

PLASMA METANEPHERINE — Ist line of INVESTIGATION

- NOT ELEVATED → PHAEO RULED OUT
- ELEVATED → URINE 24 Hrs (free) Metanepherine (IOC)
  - NOT ELEVATED → Repeat URINE 24 Hrs (free) Metanepherine
    - NEGATIVE → PHAEO RULED OUT
    - POSITIVE → Phaeo/Paraganglioma confirmed
    - EQUIVOCAL → CLONIDINE SUPRESSION TEST
  - ELEVATED → Phaeo/Paraganglioma confirmed

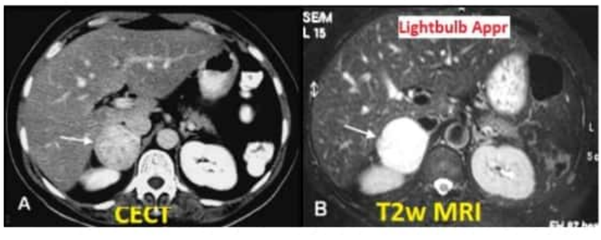
SCREENING TEST — PLASMA METANEPHERINE

CONFIRMATORY TEST — 24 hr(free) Urine Metanepherine

LOCALIZATION — MRI (IOC)

If Age <50 yrs /if Paraganglioma suspected

DOPA PET scan > MIBG scan




TREATMENT

- PRE OP: α blocker (started 2 weeks prior) → β blockers (started 2 days prior)
- SURGERY: LAPROSCOPIC ADRENALECTOMY (for < 5 cm tumors)
- POST OP: α agonist (2 weeks post op )

## DIABETES MELLITUS

### CRITERIA FOR DIAGNOSIS OF DM

Symptoms of DM + RBS ≥ 200 mg/dl

OR

Fasting plasma glucose ≥ 126 mg/dl

OR

HbA1c ≥6.5%

OR

2 hour plasma glucose ≥ 200mg/dl during an oral glucose tolerance test

| | NORMAL | IMPAIRED | DM |
|---|---|---|---|
| FBS | ADA <100<br>WHO <110 | ADA 100-125<br>WHO 110-125 | ≥126 |
| ORAL GTT | <140 | 140-199 | ≥ 200mg/dl |
| HbA1c | <5.7% | 5.7%-6.4% | ≥6.5% |

THEN WHAT TO MARK FOR FBS Normal vs Impaired values ?

If no mention about WHO or ADA then mark </>100

If WHO is mentioned then mark </>110

**Types of Diabetes**

| | DM TYPE 1 | 1.5 KETOSIS PRONE DIABETES (KPD) | 1.5 LATENT AUTOIMMUNE DIABETES IN ADULTS (LADA) | DM TYPE 2 | MATURITY ONSET DIABETES IN YOUNG (MODY) |
|---|---|---|---|---|---|
| AGE OF ONSET | <30 YRS | <30 YRS | >30 YRS | >30 YRS | 5-15 YRS AD |
| BODY HABITUS | THIN | OBESE | THIN | OBESE | THIN |
| KETONE BODIES | + | + | - | - | - |
| INSULIN RESPONSE | + | - | + | - | - |
| OHA RESPONSE | - | + | - | + | + |

## RISK FACTORS FOR TYPE 2 DM

- ✓ Family history of diabetes
- ✓ Overweight or obese
- ✓ Previously identified IFG,IGT or impaired HbA1c
- ✓ History of GDM
- ✓ Hypertension (BP>140/90)
- ✓ HDL <35 mg/dl & or TG >250 mg/dl
- ✓ PCOS or acanthosis nigrans
- ✓ History of CAD

**PHARMACOTHERAPY**

### INSULIN

**INJECTABLE INSULIN**

| | | | |
|---|---|---|---|
| ULTRASHORT/Rapid | • LISPRO<br>• ASPART<br>• GLULISINE | MONO-COMPONENT INSULIN | CONTROL POSTPRANDIAL HYPERGLYCEMIA |
| SHORT | • REGULAR | HEXAMERIC ZINC | CONTROL POSTPRANDIAL HYPERGLYCEMIA<br>IV: DKA, HYPERKALEMIA |
| INTERMIDIATE | • NPH (NEUTRAL PROTAMINE HAGEDORN) | PROTAMINE INSULIN | BASAL INSULIN (BD) |
| INTERMIDIATE | • LENTE INSULIN | MIXTURE OF 30% SEMILENTE + 70% ULTRALENTE | |
| LONG | • DETEMIR<br>• GALRGINE (24 HOURS)<br>• DEGLUDEC (42 HOURS) | GLARGINE: ACIDIC INSULIN: NEVER MIXED WITH OTHER INSULIN | BASAL INSULIN (OD) |
| | | **NASAL INSULIN** | |
| DRY POWDER INHALATION | • AFREZZA | GIVEN ALONG WITH LONG LONG ACTING INJECTABLE INSULIN | CONTROL POSTPRANDIAL HYPERGLYCEMIA |

**ADVERSE EFFECTS:** HYPOGLYCEMIA (T/T:GLUCOSE, i.m. GLUCAGON), WEIGHT GAIN, LIPODYSTROPHY, HYPOKALEMIA, EDEMA

## Anti-hyperglycemic Agents

| ACTING AT PANCREAS | ACTING AT PERIPHERAL ORGANS |
|---|---|
| • SULFONYLUREAS | • BIGUANIDES |
| • MEGLITINIDES | • ALPHA GLUCOSIDASE INHIBTORS |
| • AMYLIN ANALOGUE | • THIAZOLIDINEDIONES |
| • INCRETINS | • SGLT-2 INHIBITORS |
| • DPP-4 INHIBITOTS | |

## ANTI-HYPERGLYCEMIC AGENTS: ACTING AT PANCREAS

| ACTING AT PANCREAS | | | | | | |
|---|---|---|---|---|---|---|
| **CLASS** | **DRUGS** | **MOA** | **ROUTE** | **WEIGHT** | **HYPOGLYCEMIA** | **ADVERSE EFFECTS** |
| SULFONYLUREA | FIRST GEN:<br>CHLORPROPAMIDE<br>ACETOHEXAMIDE<br>TOLBUTAMIDE<br>TOLZOLAMIDE<br><br>SECOND GEN:<br>GLIMEPIRIDE<br>GLIPIZIDE<br>GLICLAZIDE<br>GLYBURIDE | CLOSE ATP SENSITIVE K+ CHANNEL ON BETA CELL | ORAL | GAIN | YES | HYPOGLYCEMIA<br>SULFA ALLERGY<br><br>CHLORPROPAMIDE<br>• CHOLESTASTIC JAUNDICE<br>• DISULFIRAM REACTION<br>• SIADH |
| MEGLTINIDES | REPAGLINIDE<br>NATEGLINIDE | CLOSE ATP SENSITIVE K+ CHANNEL ON BETA CELL | ORAL | GAIN | YES | HYPOGLYCEMIA<br>FLU LIKE SYMPTOMS |
| AMYLIN ANALOGUE | PRAMLINTIDE | SUPRRESS GLUCAGON AND APETITE | S/C INJ | LOSS | YES | ALLERGY |

| ACTING AT PANCREAS | | | | | | |
|---|---|---|---|---|---|---|
| **CLASS** | **DRUGS** | **MOA** | **ROUTE** | **WEIGHT** | **HYPOGLYCEMIA** | **ADVERSE EFFECTS** |
| GLP-1 ANALOGUE (INCRETINS) | EXENATIDE<br>LIRAGLUTIDE<br>LIXESENATIDE<br>ALBIGLUTIDE<br>DULAGLUTIDE<br>SEMAGLUTIDE | STIMULATE INSULIN<br>+<br>SUPRRESS GLUCAGON<br>SUPRRESS APETITE | S/C INJ | LOSS | NO | PANCREATITIS<br><br>PANCREAS AND THYROID CANCERS |
| DPP-4 INHIBITORS | SITAGLIPTIN<br>VILDAGLIPTIN<br>ALOGLIPTIN<br>LINAGLIPTIN<br>SAXAGLIPTIN | STIMULATE INSULIN<br>+<br>SUPRRESS GLUCAGON<br>SUPRRESS APETITE | ORAL | NEUTRAL | NO | INFLAMMATION<br>JOINT PAIN<br>NASOPHARYNGITIS |

## ANTI-HYPERGLYCEMIC AGENTS: ACTING AT PERIPHERAL ORGANS

| ACTING AT PERIPHERAL ORGANS | | | | | | |
|---|---|---|---|---|---|---|
| **CLASS** | **DRUGS** | **MOA** | **ROUTE** | **WEIGHT** | **HYPO GLYCE MIA** | **ADVERSE EFFECTS** |
| BIGUANIDES  | METFORMIN<br><br>PHENFORMIN | LIVER:<br>AMPK+<br>INHIBIT HEPATIC GLUCONEOGENESIS | ORAL | LOSS | NO | MEGALOBLASTIC ANEMIA<br><br>LACTIC ACIDOSIS (PHENFORMIN BANNED) |
| ALPHA GLUCOSIDASE INHIBITORS  | ACARBOSE<br>VOGLIBOSE<br>MIGLITOL | INTESTINE: REDUCE ABSORPTION OF SACCHARIDES | ORAL | NEUTRAL | NO | GIT UPSET<br><br>SUCROSE CANNOT CORRECT HYPOGLYCEMIA |
| THIAZOLIDINEDIONES  | PIOGLITAZONE<br>TROGLITAZONE<br>ROSIGLITAZONE | ADIPOSE TISSUE: PPAR-GAMMA AGONIST | ORAL | GAIN | NO | MI/CHF (ROSI: BANNED)<br>HEPATOTOXIC (TROGLITA: BANNED)<br>FRACTURES |
| SGLT-2 INHIBITORS  | CANAGLIFLOZIN<br>DAPAGLIFLOZIN<br>EMPAGLIFLOZIN | KIDNEY: INHIBIT SODIUM ABSORPTION IN PCT NEPHRON | ORAL | LOSS | NO | UTI/CYSTITIS<br>DKA<br>UROGENITAL INFECTION<br>FOURNIERS GANGRENE |

## ONE LINER MCQ's

| | |
|---|---|
| DRUGS FOR TYPE -1 DM | • INSULIN (DOC)<br>• ACARBOSE<br>• PRAMLINTIDE |
| GESTATIONAL DM | • INSULIN (DOC)<br>• METFORMIN<br>• GLYBURIDE |
| DM + PCOS | • METFORMIN |
| DM + GASTROPARESIS | • ERYHTROMYCIN: + MOTILIN RECEPTORS IN STOMACH |
| DIABETIC DIARRHEA | • CLONIDINE: ALPHA 2A + → REABSORB IONS IN INTESTINE |
| DIABETIC RETINOPATHY | • ANTI-VEGF: BEVACIZUMAB, RANIBIZUMAB, ALFIBERCEPT |
| DIABETIC NEUROPATHY | • PREGABALIN (DOC)<br>• EPALRESTAT (ALDOSE REDUCTASE INHIBITORS) |
| NO DOSE MODIFICATION IN RENAL FAILURE | • LINAGLIPTIN<br>• DULAGLUTIDE<br>• PIOGLITAZONE/ROSIGLITAZONE<br>• PRAMLINTIDE |
| ANTI-OBESITY DRUG | • LIRAGLUTIDE |

### TREATMENT GOALS

- ✓ HbA1c <7%
- ✓ Pre-prandial capillary glucose 80-130 mg/dl
- ✓ Post –prandial capillary glucose <180 mg/dl
- ✓ BP <130/80 mmHg

### FIRST LINE THERAPY –Metformin + lifestyle modifications

↓

Indicators of – Atherosclerotic cardiovascular disease (ASCVD)
- CKD
- Heart failure(HF)

↓

YES ↔ NO

### ASCVD,CKD,HF PRESENT

**ASCVD PREDOMINATES** ↔ **CKD(eGFR@30-60ml/min) or HF(LVEF<45%) PREDOMINATES**

**ASCVD PREDOMINATES**

↓ PREFERABLY *GLP-1 RA or SGLT2i*

↓ HbA1c above target

↓ Choose agents

- ✓ On GLP-1 RA add SGLT2i
- ✓ On SGLT2i add DPP-4i
- ✓ Basal Insulin
- ✓ SU

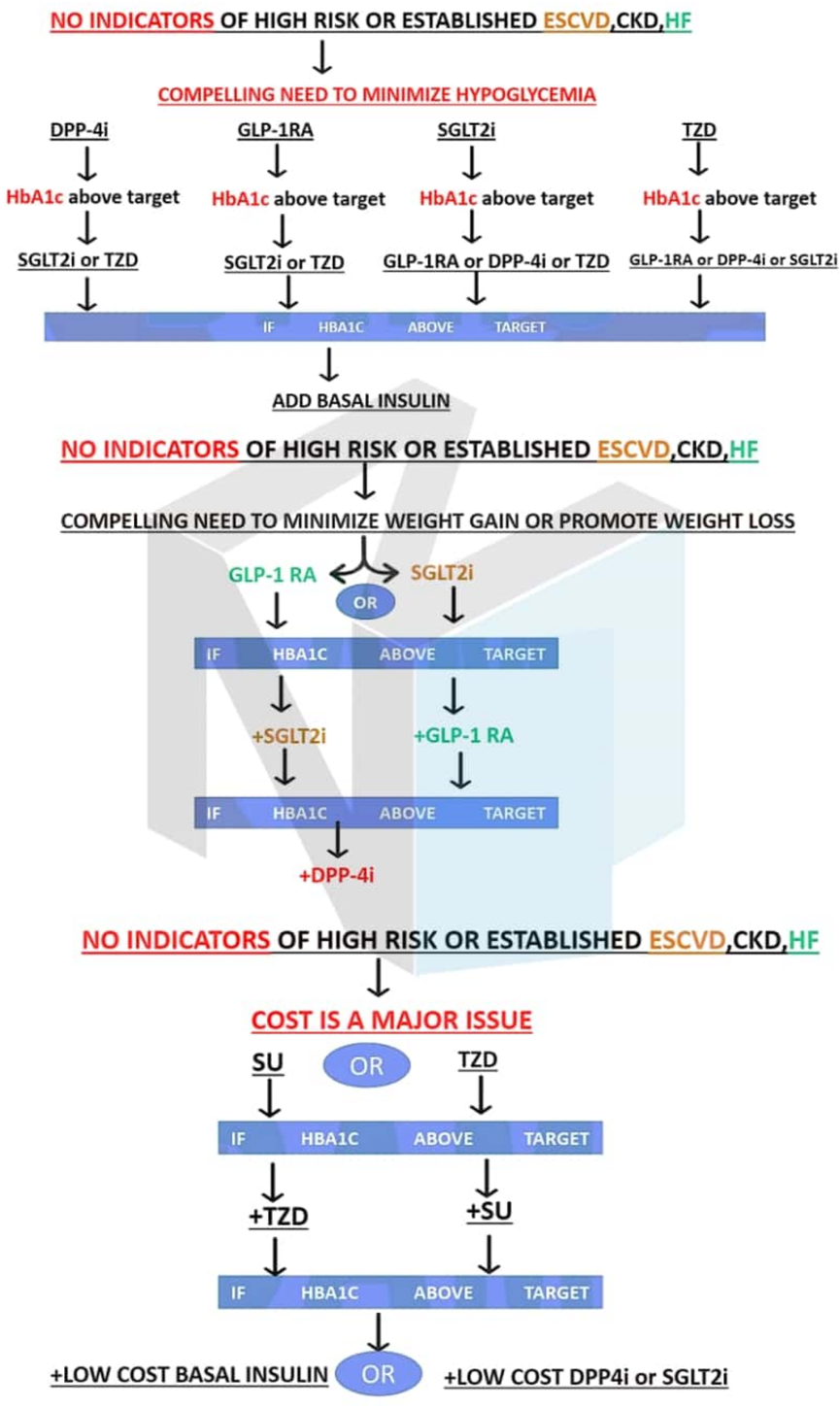
**CKD(eGFR@30-60ml/min) or HF(LVEF<45%) PREDOMINATES**

↓ PREFERABLY GLP-1RA or SGLT2i

↓ HbA1c above target

↓ Choose agents — AVOID TZD

- ✓ On GLP-1 RA add SGLT2i
- ✓ On SGLT2i add DPP-4i(not saxagliptin )
- ✓ Basal Insulin
- ✓ SU


NO INDICATORS OF HIGH RISK OR ESTABLISHED ESCVD,CKD,HF
COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA
DPP-4i
GLP-1RA
SGLT2i
TZD
HbA1c above target
HbA1c above target
HbA1c above target
HbA1c above target
SGLT2i or TZD
SGLT2i or TZD
GLP-1RA or DPP-4i or TZD
GLP-1RA or DPP-4i or SGLT2i
IF HBA1C ABOVE TARGET
ADD BASAL INSULIN
NO INDICATORS OF HIGH RISK OR ESTABLISHED ESCVD,CKD,HF
COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS
GLP-1 RA
OR
SGLT2i
IF HBA1C ABOVE TARGET
+SGLT2i
+GLP-1 RA
IF HBA1C ABOVE TARGET
+DPP-4i
NO INDICATORS OF HIGH RISK OR ESTABLISHED ESCVD,CKD,HF
COST IS A MAJOR ISSUE
SU
OR
TZD
IF HBA1C ABOVE TARGET
+TZD
+SU
IF HBA1C ABOVE TARGET
+LOW COST BASAL INSULIN
OR
+LOW COST DPP4i or SGLT2i